



Universiteit
Leiden
The Netherlands

Comparing and contrasting risk factors for heart failure in patients with and without history of myocardial infarction: data from HOMAGE and the UK Biobank

Rastogi, T.; Ho, F.K.; Rossignol, P.; Merklings, T.; Butler, J.; Clark, A.; ... ; Girerd, N.

Citation

Rastogi, T., Ho, F. K., Rossignol, P., Merklings, T., Butler, J., Clark, A., ... Girerd, N. (2022). Comparing and contrasting risk factors for heart failure in patients with and without history of myocardial infarction: data from HOMAGE and the UK Biobank. *European Journal Of Heart Failure*, 24(6), 976-984. doi:10.1002/ejhf.2495

Version: Publisher's Version
License: [Creative Commons CC BY-NC 4.0 license](https://creativecommons.org/licenses/by-nc/4.0/)
Downloaded from: <https://hdl.handle.net/1887/3567820>

Note: To cite this publication please use the final published version (if applicable).

Comparing and contrasting risk factors for heart failure in patients with and without history of myocardial infarction: data from HOMAGE and the UK Biobank

Tripti Rastogi¹, Frederick K. Ho², Patrick Rossignol¹, Thomas Merkling¹, Javed Butler³, Andrew Clark⁴, Timothy Collier⁵, Christian Delles⁶, J Wouter Jukema⁷, Stephane Heymans^{8,9,10}, Roberto Latini¹¹, Alexandre Mebazaa¹², Pierpaolo Pellicori¹³, Peter Sever¹⁴, Jan A. Staessen^{15,16}, Lutgarde Thijs¹⁷, John G. Cleland^{13,18}, Naveed Sattar⁶, Faiez Zannad¹, and Nicolas Girerd^{1*}

¹Centre d'Investigations Cliniques Plurithématique 1433, Institut Lorrain du Cœur et des Vaisseaux Louis Mathieu, CHRU de Nancy, INSERM DCAC, F-CRIN INI-CRCT, Université de Lorraine, Nancy, France; ²Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK; ³Department of Medicine, University of Mississippi School of Medicine, Jackson, MS, USA; ⁴Hull York Medical School, Castle Hill Hospital, Cottingham, UK; ⁵London School of Hygiene and Tropical Medicine, London, UK; ⁶Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; ⁷Department of Cardiology, Leiden University Medical Center, Leiden; Netherlands Heart Institute, Utrecht, The Netherlands; ⁸Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands; ⁹Department of Cardiovascular Research, University of Leuven, Leuven, Belgium; ¹⁰Netherlands Heart Institute, Utrecht, The Netherlands; ¹¹IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; ¹²Université de Paris; APHP, University Hospitals Saint Louis Lariboisière, Inserm 942 MASCOT, Paris, France; ¹³Robertson Centre for Biostatistics and Clinical Trials, Institute of Health and Wellbeing, Glasgow, UK; ¹⁴International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, UK; ¹⁵Research Institute Alliance for the Promotion of Preventive Medicine, Mechelen, Belgium; ¹⁶Biomedical Sciences Group, Faculty of Medicine, University of Leuven, Leuven, Belgium; ¹⁷Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium; and ¹⁸National Heart and Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, University of Glasgow, London, UK

Received 19 November 2021; revised 28 February 2022; accepted 29 March 2022; online publish-ahead-of-print 18 April 2022

Aims

Myocardial infarction (MI) is among the commonest attributable risk factors for heart failure (HF). We compared clinical characteristics associated with the progression to HF in patients with or without a history of MI in the HOMAGE cohort and validated our results in UK Biobank.

Methods and results

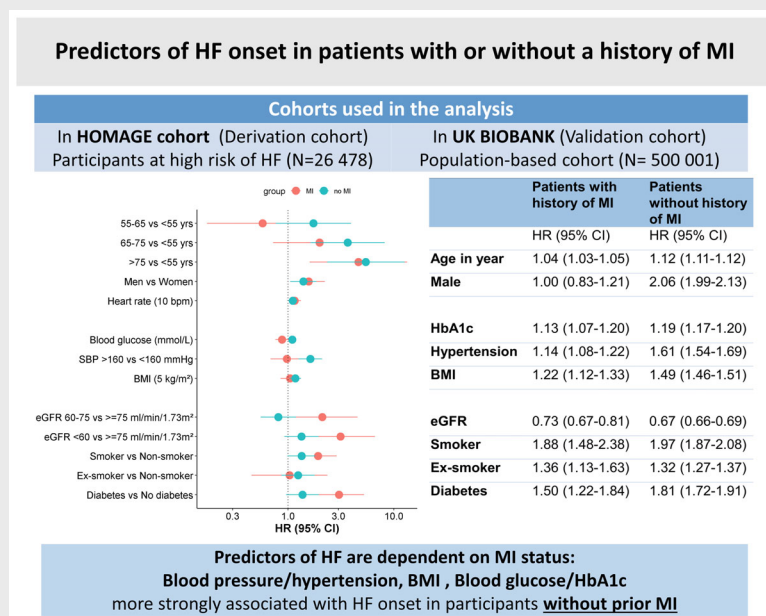
During a follow-up of 5.2 (3.5–5.9) years, 177 (2.4%) patients with prior MI and 370 (1.92%) patients without prior MI experienced HF onset in the HOMAGE cohort ($n = 26\,478$, history of MI: $n = 7241$). Older age, male sex and higher heart rate were significant risk factors of HF onset in patients with and without prior MI. Lower renal function was more strongly associated with HF onset in patients with prior MI. Higher body mass index (BMI), systolic blood pressure and blood glucose were significantly associated with HF onset only in patients without prior MI (all p for interactions <0.05). In the UK Biobank ($n = 500\,001$, history of MI: $n = 4555$), higher BMI, glycated haemoglobin, diabetes and hypertension had a stronger association with HF onset in participants without prior MI compared to participants with MI (all p for interactions <0.05).

Conclusion

The importance of clinical risk factors associated with HF onset is dependent on whether the patient has had a prior MI. Diabetes and hypertension are associated with new-onset HF only in the absence of MI history. Patients may benefit from targeted risk management based on MI history.

*Corresponding author: Centre d'Investigation Clinique Pierre Drouin -INSERM - CHRU de Nancy, Institut Lorrain du Cœur et des Vaisseaux Louis Mathieu, 4, rue du Morvan, 54500 Vandœuvre-Lès-Nancy, Nancy, France. Tel: +33 3 83157496, Fax: +33 3 83157324, Email: n.girerd@chru-nancy.fr

Graphical Abstract



Predictors of heart failure (HF) onset in patients with or without a history of myocardial infarction (MI). BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; SBP, systolic blood pressure.

Keywords

Heart failure • Myocardial infarction • Cardiovascular diseases • Survival

Introduction

Heart failure (HF) is one of the leading causes of morbidity and mortality throughout the world. With ≥ 37 million people already affected worldwide, the number will continue to rise for the next 20 years.^{1,2} Increasing life expectancy and prevalence of risk factors such as hypertension, diabetes, obesity and coronary artery disease, especially in younger populations, will further add to the steadily increasing number of HF patients.³ Despite advances in treatment, mortality rates remain particularly high with poor 5-year survival.⁴ Hence, early identification and management of risk factors is critical for preventing or delaying the onset of HF.

The implementation of preventive measures relies on the correct identification of individuals at higher risk. Several scores have been developed with the aim of identifying populations at higher risk taking into account variables such as age, sex, body mass index (BMI), lipid levels, kidney function and other comorbidities including diabetes and hypertension.^{5,6} These scores assess HF risk irrespective of the presence of prior myocardial infarction (MI), i.e. these risk score assess the HF risk based on a fixed value assigned to each risk factor including MI. However, the strength of a relation

between a risk factor and outcome might depend upon whether a patient has previously had an MI.

Different aetiologies, risk factors and pathophysiological mechanisms, in combination with concomitant diseases, render HF a complex and heterogeneous syndrome with several phenotypes.^{7,8} However, HF with history of prior MI appears distinct from HF without prior MI in many aspects, including ischaemic injury, inflammation and neurohormonal pathways involved in cardiac remodelling.⁹ Importantly, ischaemic/non-ischaemic HF is often the only characterization reported in large registries regarding HF aetiology, thus emphasizing the cardinal importance of MI history. Given the different pathophysiological background of HF with and without prior MI, classical risk factors (such as age, blood pressure, diabetes, dyslipidaemia, kidney disease, etc.) may contribute differentially to HF onset in patients with and without MI. History of MI is known to be associated with worse outcomes in patients with overt HF and could be related to MI history rather than the intrinsic prognosis of ischaemic HF.^{10,11}

We compared the clinical characteristics associated with the progression to HF in patients with or without a history of MI in patients at higher risk of HF in the Heart 'OMics' in AGEing

(HOMAGE) database and validated our results in the UK Biobank population-based cohort.

Methods

Derivation cohort

Patients included in the HOMAGE merged database were studied. Briefly, the HOMAGE database included 52 631 study participants from 21 studies from eight European countries which enrolled subjects with overt cardiovascular (CV) disease or at risk of CV disease or healthy individuals. A detailed description of the database is provided elsewhere.^{12,13}

Among this large database, patients identified to be at a higher risk for HF (i.e. without HF but with significant risk for HF based on their comorbidities/clinical history) were included in the analysis reported here.^{12,13} Patients included were originally from four separate cohorts (ASCOT, DYDA, HVC, PROSPER) in which included patients had higher risk of HF and provided sufficient follow-up to assess the incidence of HF onset (online supplementary Figure S1). Patients were included if the baseline data on age, sex, body weight and height were available. Patients who had HF at baseline or for whom follow-up data on outcome were unavailable were excluded.

Outcomes

The objective of the study was to identify whether the risk factors for HF onset differed depending on the presence (MI+) or absence of prior MI (MI-). For this objective, the selected outcome was time to HF onset as defined by hospitalization for HF. The endpoints for each study were adjudicated in the respective cohort and trials and the committee within the HOMAGE consortium retrospectively assessed the quality of endpoint adjudication for each study (online supplementary Table S1).^{5,13}

Validation cohort

The results of our analysis were replicated in UK Biobank, a large population-based, prospective observational study with 502 493 middle-aged and elderly participants from the United Kingdom.^{14,15} The health outcomes were ascertained through data linkage to hospitalization records and incident HF was defined according to the International Classification of Diseases 10th Revision codes. Subjects with prevalent HF at baseline were excluded from this analysis. Brief study design and baseline characteristics of the study participants included from the UK Biobank are presented in the online supplementary material and supplementary Table S2.

All of the studies were conducted in accordance with Good Clinical Practice guidelines and applicable national regulations and all study participants provided written informed consent.

Statistical analysis

For the descriptive analyses, continuous variables are expressed as mean \pm standard deviation (SD) for normally distributed data, or as median (Q1–Q3) for skewed data. Categorical variables are expressed as proportions (%).

Univariable Cox regression models were used to calculate the hazard ratio (HR) for HF onset associated with each risk factor. Due to differences in duration of follow-up between each cohort, the cohorts were added as strata in the Cox regression models for the HOMAGE

database. The stratified Cox proportional hazard models were used because the baseline risk and hazards in each cohort constituting the HOMAGE cohort were different and unrelated.¹⁶ Age, systolic blood pressure (SBP) and estimated glomerular filtration rate (eGFR) were categorized due to non-linearity. A backward selection procedure was applied to determine the variables to be included in the multivariable models. Total cholesterol, body weight and height were not included in the backward selection due to their high collinearity with other variables (only low density lipoprotein-cholesterol and BMI were considered). The variables found to be significantly associated with either the patients with prior MI or the patients with CV risk factors but no prior MI were then included in the final multivariable model with same variables for each group. Interactions between each risk factor and history of MI were examined in both backward selection model (interaction for unadjusted model) and fully adjusted model (additive and multiplicative interaction for adjusted model), adding multiplicative interaction terms to survival models. The discriminative value of multivariable models for HF onset was assessed using Harrell's c-index. We also ran sensitivity analyses with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) and beta-blocker use, forced in the Cox regression models. The competing risk analysis with non-HF death as competing event was conducted using Fine and Gray modification of Cox proportional hazard models. For validation analysis, a dedicated adjustment was performed to calculate HRs of risk factor associated with HF onset in UK Biobank.

Population attributable risk (PAR) percentage was calculated using the formula $PAR = Pd \cdot (HR - 1) / HR$ where Pd is the proportion of cases (i.e. HF onset) exposed to a risk factor.¹⁷ Using Bonferroni inequality, 95% confidence intervals (CIs) for PAR percentage were calculated from the general PAR formula using the lower and upper limits of the 97.5% CI for Pd and HR (online supplementary Figure S2). This metrics could be calculated for categorical variables.

Statistical analyses were performed using R 3.6.1 and 3.5.3 (<https://www.R-project.org/>). A two-sided *p*-value of <0.05 was considered statistically significant.

Results

HOMAGE cohort results

A total of 26 478 subjects were included for analysis, out of whom 7241 (27%) had a history of MI. During a median follow-up time of 5.2 (3.5–5.9) years, 2.44% ($n = 177/7241$) of participants with a history of MI and 1.92% ($n = 370/19 237$) without a history of MI developed HF.

Baseline characteristics

Participants with HF onset were older than those without, irrespective of prior MI status. Participants without prior MI who developed HF had higher SBP than participants without HF (167.5 [23.0] for HF vs. 161.3 [19.9] for non-HF) whereas the opposite was observed in patients with MI history (154.0 [23.8] for HF vs. 159.2 [19.3] for non-HF) (Table 1).

Predictors of heart failure with or without history of myocardial infarction

In multivariable analysis, male sex, older age and higher heart rate were significantly associated with increased risk of HF onset both

Table 1 Baseline characteristics in relation to history of myocardial infarction and the occurrence of heart failure during follow-up in the HOMAGE cohort

	Overall (n = 26 478)	N available	Patients with a history of MI		Patients without a history of MI ^a		p-value
			No HF onset during FU (n = 7064)	HF onset (n = 177)	No HF onset during FU (n = 18 867)	HF onset (n = 370)	
Clinical data							
Female sex	8095 (30.6)	26 478	2822 (39.9)	66 (37.3)	5090 (27.0)	117 (31.6)	<0.001
Age (years)	65.6 (9.3)	26 478	63.9 (10.3)	73.4 (7.6)	66.1 (8.8)	71.1 (7.7)	<0.001
Smoking status		26 413					<0.001
Non-smoker	11 146 (42.2)		3513 (49.8)	114 (64.4)	7368 (39.2)	151 (41.4)	
Smoker	7734 (29.3)		1806 (25.6)	43 (24.3)	5789 (30.8)	96 (26.3)	
Ex-smoker	7533 (28.5)		1733 (24.6)	20 (11.3)	5662 (30.1)	118 (32.3)	
Alcohol consumption	17 547 (67.5)	25 993	4751 (68.0)	98 (56.0)	12 480 (67.6)	218 (61.6)	0.001
Hypertension	23 711 (89.5)	26 478	6087 (86.2)	115 (65.0)	17 185 (91.1)	324 (87.6)	<0.001
Diabetes	6779 (25.6)	26 478	1096 (15.5)	34 (19.2)	5513 (29.2)	136 (36.8)	<0.001
SBP (mmHg)	160.8 (19.9)	26 407	159.2 (19.3)	154.0 (23.8)	161.3 (19.9)	167.5 (23.0)	<0.001
Heart rate (bpm)	70.8 (12.6)	26 352	70.6 (12.9)	68.8 (11.8)	70.9 (12.5)	71.8 (13.0)	0.022
BMI (kg/m ²)	27.8 [25.2, 30.8]	26 477	27.7 [25.2, 30.7]	27.2 [25.4, 30.5]	27.8 [25.2, 30.8]	28.3 [25.3, 31.6]	0.042
Laboratory data							
Blood glucose (mmol/L)	5.5 [5.0, 6.4]	24 546	5.4 [4.9, 6.0]	5.3 [4.8, 5.9]	5.6 [5.0, 6.6]	5.6 [5.0, 7.4]	<0.001
Total cholesterol (mmol/L)	5.8 (1.1)	26 435	5.9 (1.1)	5.7 (1.0)	5.8 (1.1)	5.8 (1.0)	<0.001
LDL-cholesterol (mmol/L)	3.7 (0.9)	24 273	3.8 (0.9)	3.7 (0.8)	3.7 (0.9)	3.7 (0.9)	<0.001
HDL-cholesterol (mmol/L)	1.2 [1.0, 1.5]	26 431	1.3 [1.1, 1.5]	1.2 [1.0, 1.4]	1.2 [1.0, 1.5]	1.2 [1.0, 1.5]	>0.001
Triglycerides (mmol/L)	1.5 [1.1, 2.1]	24 648	1.5 [1.1, 2.1]	1.4 [1.1, 2.0]	1.5 [1.1, 2.1]	1.5 [1.2, 2.1]	0.286
Serum creatinine (µmol/L)	96.0 [86.0, 108.0]	20 252	96.0 [85.0, 108.0]	113.0 [92.2, 132.8]	97.0 [86.0, 108.0]	99.0 [87.0, 117.0]	<0.001
eGFR (ml/min/1.73 m ²)	65.3 [55.1, 75.6]	20 252	64.9 [54.8, 75.3]	48.9 [41.4, 62.7]	65.7 [55.6, 76.0]	59.6 [47.3, 71.0]	<0.001
Medications							
ACEI/ARBs	7947 (34.8)	22 821	1933 (33.1)	62 (36.0)	5814 (35.3)	138 (40.4)	0.003
Beta-blockers	8017 (35.1)	22 821	2256 (38.6)	54 (31.4)	5610 (34.1)	97 (28.4)	<0.001
Statins	352 (37.7)	933	0 (NA)	0 (NA)	351 (37.7)	1 (50.0)	1

Data are given as n (%), mean ± standard deviation, or median [Q1–Q3].

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula); FU, follow-up; HDL, high-density lipoprotein; HF, heart failure; LDL, low-density lipoprotein; MI, myocardial infarction; SBP, systolic blood pressure.

^aPatients with cardiovascular risk factors but no prior MI.

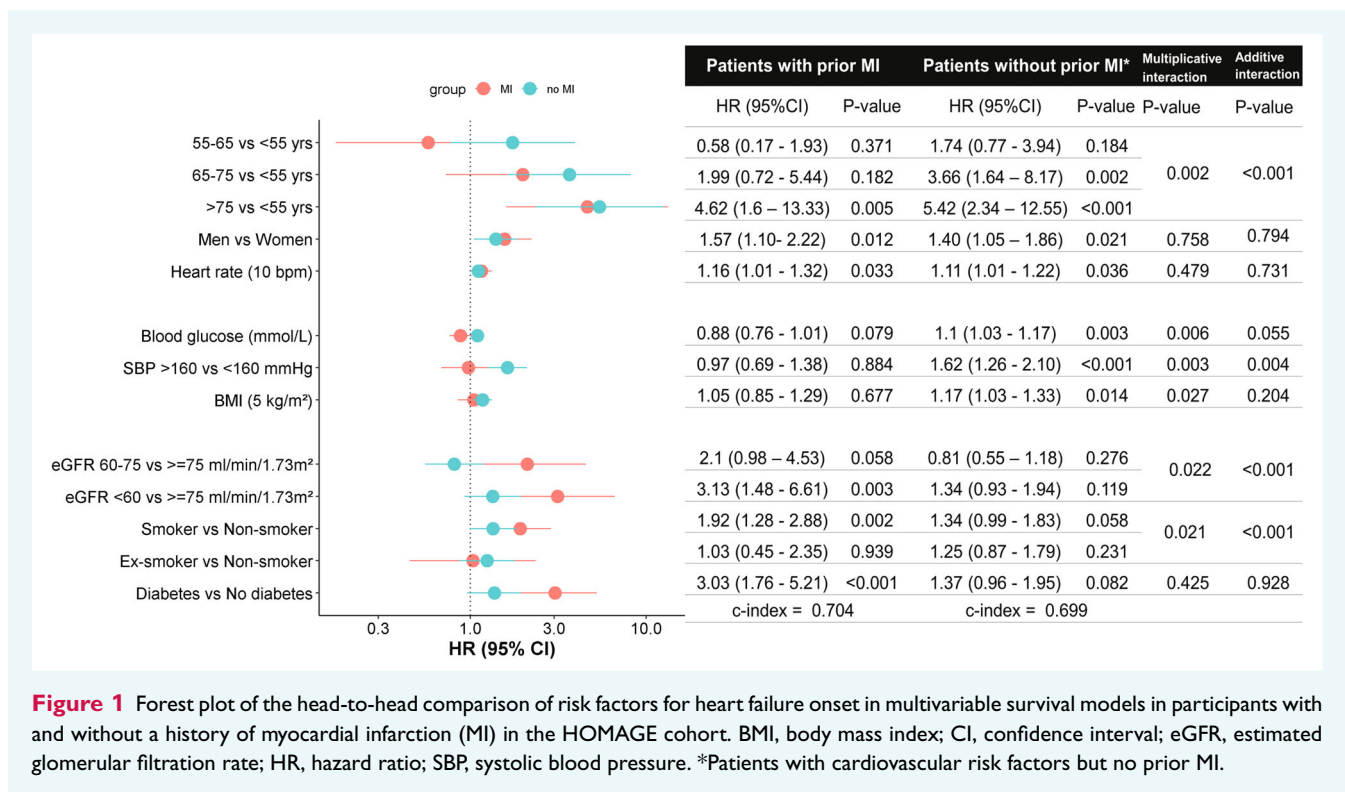


Figure 1 Forest plot of the head-to-head comparison of risk factors for heart failure onset in multivariable survival models in participants with and without a history of myocardial infarction (MI) in the HOMAGE cohort. BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SBP, systolic blood pressure. *Patients with cardiovascular risk factors but no prior MI.

in participants with, and those without, prior MI. However, older age had a stronger association with the risk of HF in participants with prior MI, as compared to those without prior MI (online supplementary Table S3).

Active smoking status was significantly associated with HF onset (HR 2.00 [1.36–2.94] $p < 0.001$) in participants with prior MI, while the association was neutral in univariable analysis in those with no prior MI. Similarly, diabetes was a predictor of HF onset only in those with prior MI. Also, worsening renal function was associated with increased risk of HF only in participants with prior MI (HR 2.0 [0.96–4.14] for 60–75 ml/min/1.73 m²; HR 3.13 [1.54–6.37] for <60 ml/min/1.73 m²; overall $p = 0.002$). In participants with no prior MI, the association was non-linear (HR 0.81 [0.55–1.18] for 60–75 ml/min/1.73 m²; HR 1.3 [0.9–1.87] for <60 ml/min/1.73 m²; overall $p = 0.006$). In contrast, higher BMI, higher SBP and higher blood glucose levels were significantly associated with HF onset and retained in multivariable models in participants without prior MI but not in participants with prior MI.

Head-to-head comparison of heart failure risk factors in multivariable models

When predictors of HF were simultaneously included in multivariable models to allow a direct comparison of the magnitude of associations in participants with and without prior MI (Figure 1 and Graphical Abstract), a similar pattern of results was observed: SBP, blood glucose and BMI were more strongly associated with incident HF in participants without prior MI (p for interaction 0.003,

0.006 and 0.027, respectively) whereas, smoking status (p for interaction 0.021) and worse renal function (p for interaction 0.002) were associated with incident HF in patients with prior MI.

The c-index of the model improved when the interaction terms of variables were added to the model (delta c-index = 0.02 [from 0.70 to 0.72]; $p = 0.001$). Similarly, a modest, but still significant, improvement of c-index was observed in the validation cohort (delta c-index = 0.004 [from 0.797 to 0.802]; $p = 0.01$).

Forcing for ACEi/ARB and beta-blocker use into the model did not affect the results (online supplementary Table S4).

In the competing risk analysis model, the pattern of association of variable and HF onset was similar to multivariable model without competing risk. However, sex was neutrally associated with HF onset in patients without prior MI in the competing risk model (online supplementary Table S6).

The attributable risk of high SBP was markedly higher in patients without prior MI (online supplementary Figure S2).

Validation analysis in the UK Biobank study

From the UK Biobank study, 500 001 subjects were included in the validation analysis, of whom 4555 (0.91%) had a history of MI at baseline. The validation cohort participants were younger (~9 years) and fewer participants had hypertension and diabetes compared to participants in the HOMAGE database. Among people with prior MI, 14.9% (680/4555) developed incident HF while 2.7% (13 536/495 446) participants without prior MI developed HF over a median (Q1–Q3) follow-up of 11.8 (11.1–12.5) years.

Table 2 Multivariable Cox regression models for heart failure event with or without history of myocardial infarction in the UK Biobank study

	Patients with history of MI		Patients without history of MI		p-value for interaction
	HR (95% CI)	p-value	HR (95% CI)	p-value	
Age in years	1.04 (1.03–1.05)	< 0.0001	1.12 (1.11–1.12)	< 0.0001	< 0.0001
Male sex	1.00 (0.83–1.21)	0.97	2.06 (1.99–2.13)	< 0.0001	< 0.0001
eGFR	0.73 (0.67–0.81)	< 0.0001	0.67 (0.66–0.69)	< 0.0001	< 0.0001
HbA1c	1.13 (1.07–1.20)	< 0.0001	1.19 (1.17–1.20)	< 0.0001	0.03
Hypertension	1.14 (1.08–1.22)	0.29	1.61 (1.54–1.69)	< 0.0001	0.0005
BMI	1.22 (1.12–1.33)	< 0.0001	1.49 (1.46–1.51)	< 0.0001	0.0005
Smoker	1.88 (1.48–2.38)	< 0.0001	1.97 (1.87–2.08)	< 0.0001	0.59
Ex-smoker	1.36 (1.13–1.63)	0.0009	1.32 (1.27–1.37)	< 0.0001	0.74
Type 2 diabetes	1.50 (1.22–1.84)	0.0001	1.81 (1.72–1.91)	< 0.0001	0.03

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; MI, myocardial infarction.

Increasing age and smoking were significantly associated with increased risk of HF in people with and without prior MI. A higher BMI, glycated haemoglobin (HbA1c), diabetes and hypertension had a stronger association with HF onset in participants without prior MI compared to participants with prior MI (*p* for interaction: 0.0005, 0.03, 0.03 and 0.0005, respectively) (Table 2 and online supplementary Table S5). In addition, male sex was significantly associated with a higher risk of HF onset only in participants with prior MI but not in participants without MI (*p* for interaction < 0.0001) and lower eGFR was more strongly associated with higher risk of HF onset in patients with prior MI (HR 0.73 [0.67–0.81] vs 0.67 [0.66–0.69], *p* for interaction < 0.0001).

Discussion

In this pooled cohort study of patients at higher risk of developing HF, we found that the pattern of association of risk factors with HF was dependent on the presence of prior MI. Increasing age, male sex and higher heart rate were associated with HF onset irrespective of MI history, and should consequently be perceived as stable and ubiquitous risk factors for HF onset. Poorer renal function predisposed to HF onset more in patients with MI. Blood pressure/hypertension, BMI and blood glucose/HbA1c were more strongly associated with HF onset in participants with CV risk but no prior MI both in the HOMAGE cohort and UK Biobank cohort. Our results are in line with previous reports suggesting that metabolic factors and hypertension are more associated with HF with preserved ejection fraction (HFpEF) than HF with reduced ejection fraction (HFrEF).^{18,19} Importantly, despite the differences in baseline characteristics and risk factors in the HOMAGE (participants at high risk of HF) and UK Biobank study (population-based cohort), we saw a strikingly similar pattern of association between metabolic- and hypertension-related factors and new onset HF in patients without MI.

These results consequently suggest that, as in patients with overt HF, prior MI should be a variable systematically emphasized in epidemiological studies focusing on the prediction of HF onset.

Importantly, metabolic- and hypertension-related factors have a greater impact on HF onset in the absence of prior MI, and their prevention/treatment should consequently be particularly optimized in people who have not had an MI.

Risk factors more associated with heart failure onset in the participants with prior myocardial infarction

Diabetes, renal dysfunction and smoking status were strong predictors of HF onset in the prior MI group in the HOMAGE cohort. Our results are in keeping with previous studies where diabetes and renal dysfunction were found to be an important determinant of HF onset (twofold increase in risk of HF) in post-MI patients.^{20,21} This differential impact is not currently captured in the risk scores calculated with multivariable risk models where diabetes is associated with a fixed risk estimate irrespectively of MI history. However, it is noteworthy to mention that diabetes was more strongly associated with participants with no prior MI in the validation cohort. The difference of association of diabetes in derivation and validation may be due to differences in the population requiring insulin for management of diabetes. Previous studies have shown that CV mortality is substantially higher in patients with prior MI and insulin-treated diabetes compared to patients with prior MI and diabetes treated with oral medications due to more frequent presence of atherosclerotic disease in patients with diabetes requiring insulin.²² Yet, we did not have access to diabetes treatment in the HOMAGE cohort, and could consequently not verify this hypothesis.

Smoking is significantly associated with new-onset HF following MI, possibly due to increased myocardial injury and myocardial haemorrhage, even though smokers seemingly had a better risk profile than non-smokers.^{23,24} However, smoking status was similarly associated with incident HF regardless of prior MI in the validation cohort and the pattern of association seen for smoking in HOMAGE (*p* for interaction = 0.021) was not replicated in

the UK Biobank (p for interaction = 0.59). This difference was perhaps due to differences in the baseline smoking behaviour of the participants in the two cohorts.

The pattern of association between male sex and HF onset was dissimilar between the two cohorts. In the HOMAGE cohort, male sex was similarly associated with higher risk in both groups whereas, in the UK Biobank, male sex was associated significantly with participants with CV risk but no prior MI. The difference in the statistical association could be due to an overall higher proportion of men in HOMAGE compared to UK Biobank (60% vs. 45%).

Renal impairment/chronic kidney disease (CKD) is frequently associated with patients with prior MI. Although the exact mechanism linking HF and CKD is not known, it has been speculated that neurohormonal activation, renal hypoperfusion, increased inflammatory markers involved in myocardial repair, anaemia and volume overload contribute towards progressive HF, especially post-MI. Similar findings were reported in an observational study where patients with HFrEF and CKD had higher frequency of a prior MI compared to patients with HFpEF.²⁵ Further, CKD was more strongly associated with HFrEF in comparison of HFpEF. Besides pathophysiological mechanisms, CKD restricts the use of optimal dosage of renin–angiotensin inhibitors post-MI, thereby increasing the risk of HF. These findings imply that reno-protection is particularly important in patients with prior MI.

Risk factors more strongly associated with heart failure onset in participants with cardiovascular risk but no prior myocardial infarction

Our study found hypertension as a strong risk factor for HF onset in patients with CV risk but no prior MI. Similarly, an analysis of the Framingham Heart Study cohort previously demonstrated that hypertension is the most important risk factor associated with HF onset.²⁶ Our results highlight that the magnitude of the association between blood pressure and incident HF is far greater in patients without prior MI than in patients with prior MI. There was no relation between SBP and incident HF in patients with prior MI, perhaps because low SBP was due to reduced left ventricular function and, hence, greater risk of HF onset.²⁷ Importantly, in the present analysis, higher SBP (in HOMAGE) and history of hypertension (in UK Biobank) was not associated with an increased risk of incident HF in patients with a prior MI. Previous studies have shown that lower blood pressure could be related to greater left ventricular dilatation following MI, thus increasing the risk of subsequent HF.^{27,28} There is a blood pressure paradox in patients with HFrEF: higher blood pressure appears to be 'protective'.^{29,30} However, the paradox has been described only *after* HF onset, whereas we focus here on the pre-HF period.

Metabolic factors such as BMI and blood glucose were stronger predictors of HF onset in patients with CV risk but no prior MI in our study. Similarly, the validation analysis found that hypertension, diabetes and higher BMI were more strongly related to HF onset without prior MI. Similar findings were observed in a study combining data from middle-aged men and women from four different

American CV disease cohorts,³¹ in which participants who did not have any of the three risk factors (hypertension, obesity and diabetes) had a substantially lesser risk of HF, thus placing greater emphasis on metabolic factors in the genesis of HF in patients without MI. In the presence of a prior MI, a lower prevalence of metabolic risk factors is perhaps sufficient to trigger remodelling and tip the patient into HF. In addition, previous studies have reported an obesity paradox where lower to normal BMI is associated with poorer CV outcome post-MI compared to overweight patients perhaps due to a younger age of disease presentation and other confounding variables such as smoking and cardiorespiratory fitness.^{32,33}

Diabetes, hypertension and obesity are associated with impaired myocardial energy consumption, cardiac hypertrophy and oxidative damage. These mechanisms play a role in impaired relaxation leading to diastolic dysfunction.³⁴ Further, a recent study found that diabetes/elevated blood glucose is reported to be associated with increased levels of high-sensitivity cardiac troponin T suggesting sub-myocardial damage.³⁵ It seems that even in absence of direct myocardial damage (prior MI), considerable injury to the heart is caused by cardiometabolic risk factors.

Risk scores and risk prediction models

A number of scores have been developed for predicting the risk of HF. The Framingham Study congestive HF (1999) risk score based on key clinical features was the first to provide estimates of the 4-year probability of HF.³⁶ Subsequently, the ARIC HF risk calculator, the Health ABC risk score, the PCP-HF calculator and the HOMAGE score were developed based on clinical and laboratory features.^{5,6,37,38} Importantly, however, none of these scores differentiates HF prediction according to history of MI. Having access to a large dataset enabled us to assess interactions with MI history efficiently. Interaction p -values were significant (for both additive and multiplicative interaction) for many factors and addition of interaction terms led to a modest but significant improvement of the c-index in both derivation and validation cohorts. Further, we found similar pattern of association and significant interaction p -values in competing risk model with non-HF death as competing risk factor. Fine and Gray competing risk model may have predicted an upward bias in estimating HRs for each risk factor; however, directionality of the association and relative magnitudes of risk factors can be inferred.³⁹ Overall, these findings suggest substantial differences between the association of each risk factor in patients with or without prior MI – something that has not been previously emphasized.

Limitations

There are several limitations to our study. First, the results are subject to biases inherent to all observational cohort studies. Second, the included cohorts featured certain differences in inclusion criteria and length of the follow up-period. For example, the DYDA study considered MI as an exclusion criterion while the ASCOT cohort had a longer follow-up time than the other three cohorts. However, all models were adjusted for clinical characteristics.

Third, the diagnosis of HF was not based on the Framingham criteria but rather on hospitalization for HF. Hence, non-hospitalized HF patients were not labelled as HF in the current analysis. Moreover, differences in HF hospitalization due to different hospital admissions policy, treating physicians, adherence to guidelines for therapy occur in different cohorts. Further, we do not have data regarding how long ago MI happened before the recruitment in the cohort and if there were recurrent MIs during follow-up. Fourth, it is possible that some of the patients enrolled had had clinically silent MIs and were consequently included in the CV risk but no prior MI group, thus diluting the difference between the two groups. In addition, the overall SBP in the HOMAGE database was high due to the phenotype of patients included in the original cohorts aggregated within the HOMAGE consortium. Therefore, we used a cut-off of 160 mmHg in the HOMAGE cohort given the structure of the data. However, the results were similar in the UK Biobank using the classic definition for hypertension. Finally, left ventricular ejection fraction at the time of HF onset was not available; we cannot consequently provide HFrEF or HFpEF specific associations. Whether the pattern of association we observed is primarily driven by a subtype of HF (i.e. HFrEF or HFpEF) should be further studied in the future.

Research and clinical implications

Our results suggest that 'classical' risk factors for HF carry a different weighting depending on the clinical setting. This fact has not been sufficiently emphasized previously. In light of our results, a history of prior MI should be particularly highlighted in epidemiological studies focusing on predictors of HF onset, as is done in studies performed in patients with overt HF. In addition, the modifying impact of MI on HF predictors should be systematically assessed in future reports. A personalized HF risk stratification may help in designing preventive strategies depending on the clinical setting. In patients without MI, hypertension treatment and the control of metabolic features appear to be of much greater importance. These results could help in the prioritization of healthcare interventions in the prevention of HF.

Conclusions

The importance of clinical risk factors and the increase in subsequent mortality risk following HF onset is dependent on the presence or absence of a history of prior MI. These results suggest that patients should be differentiated in terms of risk assessment based on their history of prior MI and may ultimately benefit from different targeted interventions to prevent HF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

The research leading to these results has received funding from the European Union Commission's Seventh Framework Programme

under grant agreement No. 305507 (HOMAGE [Heart Omics in Ageing consortium]). UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government and the British Heart Foundation. Dr Girerd, Rossignol, and Zannad are supported by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004), by the French PIA project Lorraine Université d'Excellence GEENAGE (ANR-15-IDEX-04-LUE) programs, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP. Dr Sattar and Dr Cleland are supported by the British Heart Foundation Research Excellence Award (RE/18/6/34217).

Conflict of interest: P.R. received personal fees (consulting) for Idorsia and G3P, honoraria from AstraZeneca, Bayer, CVRx, Fresenius, Grunenthal, Novartis, NovoNordisk, Servier, StealthPeptides, Ablative Solutions, Corvidia, Relypsa and Vifor Fresenius Medical Care Renal Pharma, outside the submitted work, and is the cofounder of CardioRenal. J.B. is a consultant to Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Berlin Cures, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, G3 Pharmaceutical, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, and Vifor. J.A.S. reports funding from APPREMED (URL: www.appremed.org) and a non-binding grant from OMRON Healthcare Co., Ltd., Kyoto, Japan. F.Z. reports steering committee personal fees from Applied Therapeutics, Bayer, Boehringer, Boston Scientific, Novartis, Janssen and CVRx, advisory board personal fees from, AstraZeneca, Vifor Fresenius, Cardior, Cereno pharmaceutical and Merck, stock options at G3Pharmaceutical, and being the founder of CardioRenal and CVCT. N.G. reports honoraria from Novartis, AstraZeneca, Boehringer and Vifor. All other authors have nothing to disclose.

References

- Ziaeeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol.* 2016;**13**:368–78.
- Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* 2017;**14**:591–602.
- Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol.* 2018;**15**:230–40.
- Shah KS, Xu H, Matsouka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol.* 2017;**70**:2476–86.
- Jacobs L, Efremov L, Ferreira JP, Thijs L, Yang WY, Zhang ZY, et al.; Heart "OMics" in AGEing (HOMAGE) Investigators. Risk for incident heart failure: a subject-level meta-analysis from the Heart "OMics" in AGEing (HOMAGE) study. *J Am Heart Assoc.* 2017;**6**:e005231.
- Khan SS, Ning H, Shah SJ, Yancy CW, Carnethon M, Berry JD, et al. 10-year risk equations for incident heart failure in the general population. *J Am Coll Cardiol.* 2019;**73**:2388–97.
- Shah SJ, Kitzman DW, Borlaug BA, Van Heerebeek L, Zile MR, Kass DA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation.* 2016;**134**:73–90.
- Ho JE, Enserro D, Brouwers FP, Kizer JR, Shah SJ, Psaty BM, et al. Predicting heart failure with preserved and reduced ejection fraction: the international collaboration on heart failure subtypes. *Circ Heart Fail.* 2016;**9**:e003116.
- Bhatt AS, Ambrosy AP, Velazquez EJ. Adverse remodeling and reverse remodeling after myocardial infarction. *Curr Cardiol Rep.* 2017;**19**:71.
- Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Precipitating clinical factors, heart failure characterization, and outcomes in

- patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. *JACC Heart Fail.* 2016;**4**:464–72.
11. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiane M, Greenberg BH, et al.; OPTIMIZE-HF Investigators and Hospitals. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med.* 2008;**168**:847–54.
 12. Ferreira JP, Girerd N, Pellicori P, Duarte K, Girerd S, Pfeffer MA, et al.; Heart 'OMics' in AGEing (HOMAGE) Initiative and the High-Risk Myocardial Infarction Database Initiative. Renal function estimation and Cockcroft-Gault formulas for predicting cardiovascular mortality in population-based, cardiovascular risk, heart failure and post-myocardial infarction cohorts: the Heart 'OMics' in AGEing (HOMAGE) and the High-Risk Myocardial Infarction Database Initiatives. *BMC Med.* 2016;**14**:181.
 13. Jacobs L, Thijs L, Jin Y, Zannad F, Mebazaa A, Rouet P, et al. Heart 'OMics' in AGEing (HOMAGE): design, research objectives and characteristics of the common database. *J Biomed Res.* 2014;**28**:349–59.
 14. Fry D, Almond R, Moffat S, Gordon M, Singh P. UK Biobank Biomarker Project: Companion Document to Accompany Serum Biomarker Data. Available from: https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum_biochemistry.pdf (accessed 6 April 2022).
 15. Ho FK, Celis-Morales C, Gray SR, Petermann-Rocha F, Lyall D, Mackay D, et al. Child maltreatment and cardiovascular disease: quantifying mediation pathways using UK Biobank. *BMC Med.* 2020;**18**:143.
 16. Rossello X, González-Del-Hoyo M. Survival analyses in cardiovascular research, part II: statistical methods in challenging situations. *Rev Esp Cardiol (Engl Ed).* 2022;**75**:77–85.
 17. Natarajan S, Lipsitz SR, Rimm E. A simple method of determining confidence intervals for population attributable risk from complex surveys. *Stat Med.* 2007;**26**:3229–39.
 18. Elgendy IY, Mahtta D, Pepine CJ. Medical therapy for heart failure caused by ischemic heart disease. *Circ Res.* 2019;**124**:1520–35.
 19. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res.* 2019;**124**:1598–617.
 20. Patel N, Chen O, Donahue C, Wang B, Fang Y, Donnino R, et al. Impact of diabetes on heart failure incidence in adults with ischemic heart disease. *J Diabetes Complications.* 2017;**31**:1597–601.
 21. Wellings J, Kostis JB, Sargsyan D, Cabrera J, Kostis WJ. Risk factors and trends in incidence of heart failure following acute myocardial infarction. *Am J Cardiol.* 2018;**122**:1–5.
 22. Rossello X, Ferreira JP, McMurray JJ, Aguilar D, Pfeffer MA, Pitt B, et al. Editor's choice – Impact of insulin-treated diabetes on cardiovascular outcomes following high-risk myocardial infarction. *Eur Heart J Acute Cardiovasc Care.* 2019;**8**:231–41.
 23. Haig C, Carrick D, Carberry J, Mangion K, Maznyczka A, Wetherall K, et al. Current smoking and prognosis after acute ST-segment elevation myocardial infarction: new pathophysiological insights. *JACC Cardiovasc Imaging.* 2019;**12**:993–1003.
 24. Gerber Y, Rosen LJ, Goldbourt U, Benyamini Y, Drory Y. Smoking status and long-term survival after first acute myocardial infarction: a population-based cohort study. *J Am Coll Cardiol.* 2009;**54**:2382–7.
 25. Löfman I, Szummer K, Dahlström U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur J Heart Fail.* 2017;**19**:1606–14.
 26. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA.* 1996;**275**:1557–62.
 27. Regnault V, Lagrange J, Pizard A, Safar ME, Fay R, Pitt B, et al. Opposite predictive value of pulse pressure and aortic pulse wave velocity on heart failure with reduced left ventricular ejection fraction: insights from an Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) sub-study. *Hypertension.* 2014;**63**:105–11.
 28. Dobre D, Kjekshus J, Rossignol P, Girerd N, Benetos A, Dickstein K, et al. Heart rate, pulse pressure and mortality in patients with myocardial infarction complicated by heart failure. *Int J Cardiol.* 2018;**271**:181–5.
 29. Ambrosy AP, Vaduganathan M, Mentz RJ, Greene SJ, Subačius H, Konstam MA, et al. Clinical profile and prognostic value of low systolic blood pressure in patients hospitalized for heart failure with reduced ejection fraction: insights from the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial. *Am Heart J.* 2013;**165**:216–25.
 30. Ather S, Chan W, Chillar A, Aguilar D, Pritchett AM, Ramasubbu K, et al. Association of systolic blood pressure with mortality in patients with heart failure with reduced ejection fraction: a complex relationship. *Am Heart J.* 2011;**161**:567–73.
 31. Ahmad FS, Ning H, Rich JD, Yancy CW, Lloyd-Jones DM, Wilkins JT. Hypertension, obesity, diabetes, and heart failure-free survival: the Cardiovascular Disease Lifetime Risk Pooling Project. *JACC Heart Fail.* 2016;**4**:911–9.
 32. Lavie CJ, Arena R, Alpert MA, Milani RV, Ventura HO. Management of cardiovascular diseases in patients with obesity. *Nat Rev Cardiol.* 2018;**15**:45–56.
 33. Stienen S, Ferreira JP, Girerd N, Duarte K, Lamiral Z, McMurray JJV, et al.; High-Risk Myocardial Infarction Database Initiative. Mean BMI, visit-to-visit BMI variability and BMI changes during follow-up in patients with acute myocardial infarction with systolic dysfunction and/or heart failure: insights from the High-Risk Myocardial Infarction Initiative. *Clin Res Cardiol.* 2019;**108**:1215–25.
 34. von Bibra H, Paulus W, St John Sutton M. Cardiometabolic syndrome and increased risk of heart failure. *Curr Heart Fail Rep.* 2016;**13**:219–29.
 35. Selvin E, Lazo M, Chen Y, Shen L, Rubin J, McEvoy JW, et al. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. *Circulation.* 2014;**130**:1374–82.
 36. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PWF, Levy D. Profile for estimating risk of heart failure. *Arch Intern Med.* 1999;**159**:1197–204.
 37. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, et al.; Health ABC Study. Incident heart failure prediction in the elderly: the Health ABC Heart Failure score. *Circ Heart Fail.* 2008;**1**:125–33.
 38. Agarwal SK, Chambless LE, Ballantyne CM, Astor B, Bertoni AG, Chang PP, et al. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) study. *Circ Heart Fail.* 2012;**5**:422–9.
 39. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med.* 2017;**36**:4391–400.